Bacteria acting with tumorigenic chaperones

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Even when restricted, only to those 11 infectious agents that have been classified as well established carcinogenic agents in humans by the International Agency for Research on Cancer, roughly 15% of human cancers are thought to be caused by infectious agents (Plummer et al. 2016) with cervical cancer induced by human papilloma viruses (HPV) constituting the most well-known example. Aside from viruses, some bacteria also seem to play a causal role as tumor-promoting agents and some of them are not only known as pathogens but also constituting part of the normal microbiota of several tissues and organs (Libertucci and Young 2019). The number of newly diagnosed patients with cancers attributable to *Helicobacter pylori* alone in 2012 has been estimated to be 770,000 worldwide (Plummer et al. 2016).

As to their ability to induce tumorigenic transformation, the exact mechanisms of interaction of procaryotes and their hosts still remain elusive in the majority of cases. In a recent PNAS article, Davide Zella and coworkers describe a novel mechanism by which bacteria can alter the genomic stability of their host's cells thereby promoting tumorigenic transformation.

Zella et al. 2018 hypothesized that the ability of a *Mycoplasma fermentans* strain to induce lymphomagenesis in an SCID mouse model might be due to a p53-dependent mechanism akin to lymphomagenesis in uninfected p53^{-/-} SCID mice. Further experiments, e.g., using human cells infected with *M. fermentans*, confirmed this hypothesis. Results indicated that mycoplasma-derived chaperone protein DnaK, belonging to the HSP70 protein family involved in protein-interaction networks (Ghazaei 2017), binds to Ubiquitin Specific Peptidase 10 (USP10) and prevents its deubiquitinating activity. Thus DnaK is reducing p53 stability

and its ability to assure genomic stability and to prevent tumorigenesis. In addition, DnaK also directly impaired the catalytic activity of poly (ADP-ribose) polymerase (PARP) proteins involved in DNA repair. Moreover, uninfected bystander cells were found to take up exogenous DnaK possibly enabling bacteria to destabilize their host's genome even in a paracrine manner. By comparing the DnaK amino acid sequence with that of other bacteria, the authors found a striking similarity with those of *Helicobacter pylori*, *Fusobacterium nucleatum*, and *Chlamydia trachomatis*, i.e., bacteria known to be associated with a variety of human cancers. In contrast, these latter DnaKs were found to be phylogenetically distinct from *E. coli* DnaK which accordingly does not lead to decreased p53 functions.

The described mechanism offers a straightforward explanation for associations observed between certain bacteria and tumorigenesis and certainly warrants further investigations. In addition, the findings may have considerable clinical implications. For example, bacteria endowed with a “type” of DnaK reducing p53-activity may enhance the effects of chemical mutagens and ionizing agents and may interact with other infectious agents thus initiating cancer. Of note, e.g., *M. genitalium* may increase the risk of high-risk HPV infections (Ye et al. 2018). On the other hand, these bacteria may also interfere with the action of some anticancer drugs with an activity depending upon an intact p53 network.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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